Global Optimization: For Some Problems, There's HOPE

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Applied Mathematics and Scientific Computation

Outline

- Problem and Existing Methods
- Homotopy Optimization Methods
- Protein Structure Prediction Problem
- Numerical Experiments
- Conclusions/Future Directions

Problem

- Solve the unconstrained minimization problem

$$f(x^*) = \min_{x \in \mathbb{R}^n} f(x) \qquad (f : \mathbb{R}^n \to \mathbb{R})$$

- Function Characteristics
  - Solution exists, smooth ($f \in C^2(\mathbb{R}^n, \mathbb{R})$)
  - Complicated (multiple minima, deep local minima)
  - Good starting points unknown/difficult to compute
- Challenges
  - Finding solution in reasonable amount of time
  - Knowing when solution has been found

Some Existing Methods

- Exhaustive/enumerative search
- Stochastic search [Spall, 2003]; adaptive [Zabinsky, 2003]
- "Globalized" local search [Pinter, 1996]
- Branch and bound [Horst and Tuy, 1996]
- Genetic/evolutionary [Voss, 1999]
- Smoothing methods [Piela, 2002]
- Simulated annealing [Salamon, et al., 2002]
- Homotopy/continuation methods [Watson, 2000]

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Homotopy Methods for Solving Nonlinear Equations

- Goal
  - Solve complicated nonlinear target system

$$f_1(x) = 0, \qquad (f_1 : \mathbb{R}^n \to \mathbb{R}^n)$$

- Steps to solution
  - Easy template system: $f_0(x^0) = 0 \quad (x^0 \ \ known)$
  - Define a continuous homotopy function:
    - $h(x, \lambda) = \begin{cases} f_0(x), & \text{if } \lambda = 0 \\ f_1(x), & \text{if } \lambda = 1 \end{cases}$
    - Example (convex): $h(x, \lambda) = (1 - \lambda) f_0(x) + \lambda f_1(x)$
  - Trace path of $h(x, \lambda) = 0$ from $\lambda = 0$ to $\lambda = 1$

Homotopy Optimization Methods (HOM)

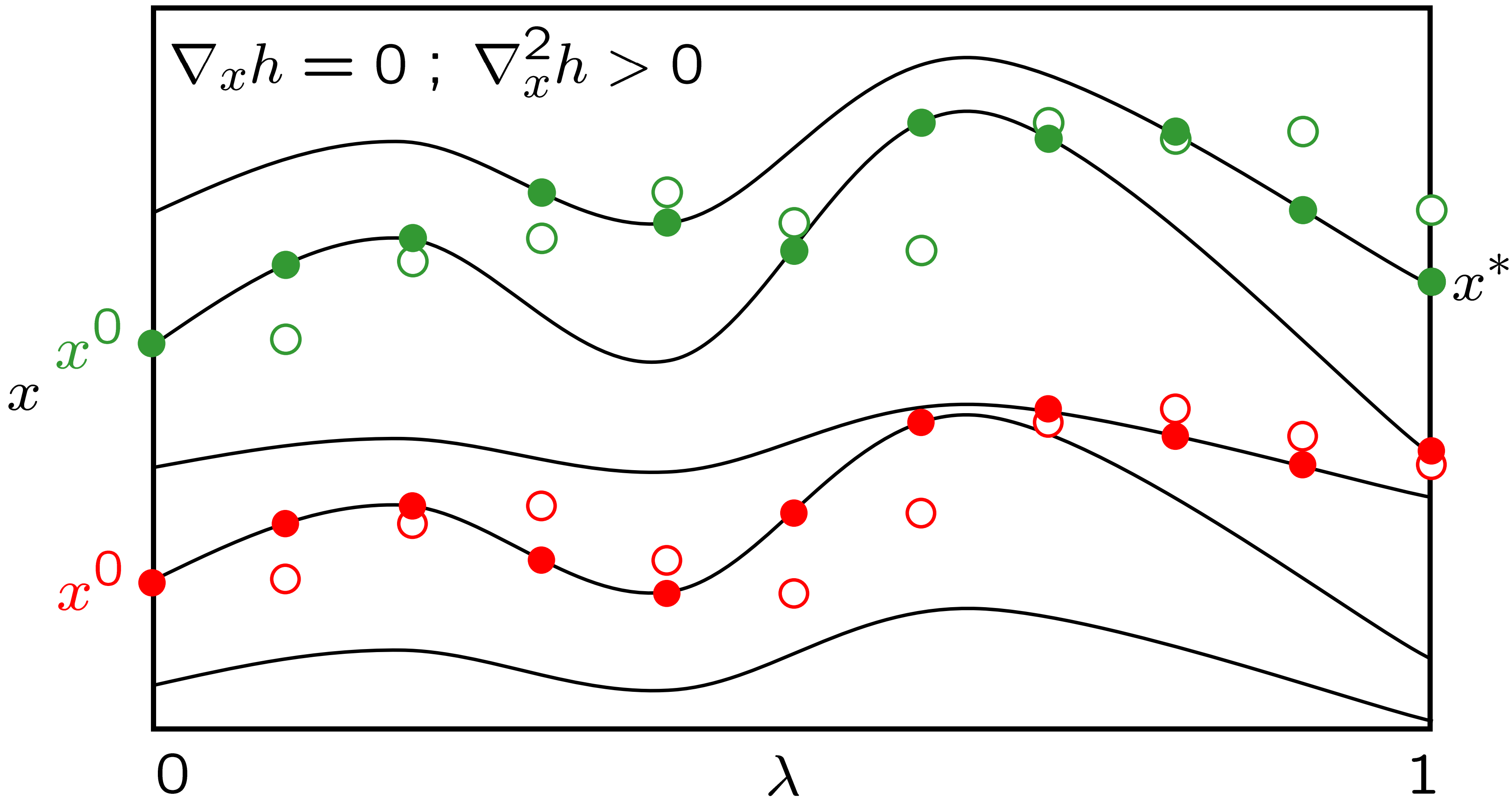
- Goal
  - Minimize complicated nonlinear target function

$$\min_{x \in \mathbb{R}^n} f_1(x), \qquad (f_1 : \mathbb{R}^n \to \mathbb{R})$$

- Steps to solution
  - Easy template function: $f_0(x^0) = \min_{x \in \mathbb{R}^n} f_0(x)$
  - Define a continuous homotopy function:
    - $h(x, \lambda) = \begin{cases} f_0(x), & \text{if } \lambda = 0 \\ f_1(x), & \text{if } \lambda = 1 \end{cases}$
    - Example (convex): $h(x, \lambda) = (1 - \lambda) f_0(x) + \lambda f_1(x)$
  - Produce sequence of minimizers of $h(x, \lambda)$ w.r.t. x starting at $\lambda = 0$ and ending at $\lambda = 1$

Illustration of HOM

$$x^* = \min_{x \in \mathbb{R}} f_1(x) \qquad h(x,\lambda) = (1-\lambda) f_0(x) + \lambda f_1(x)$$



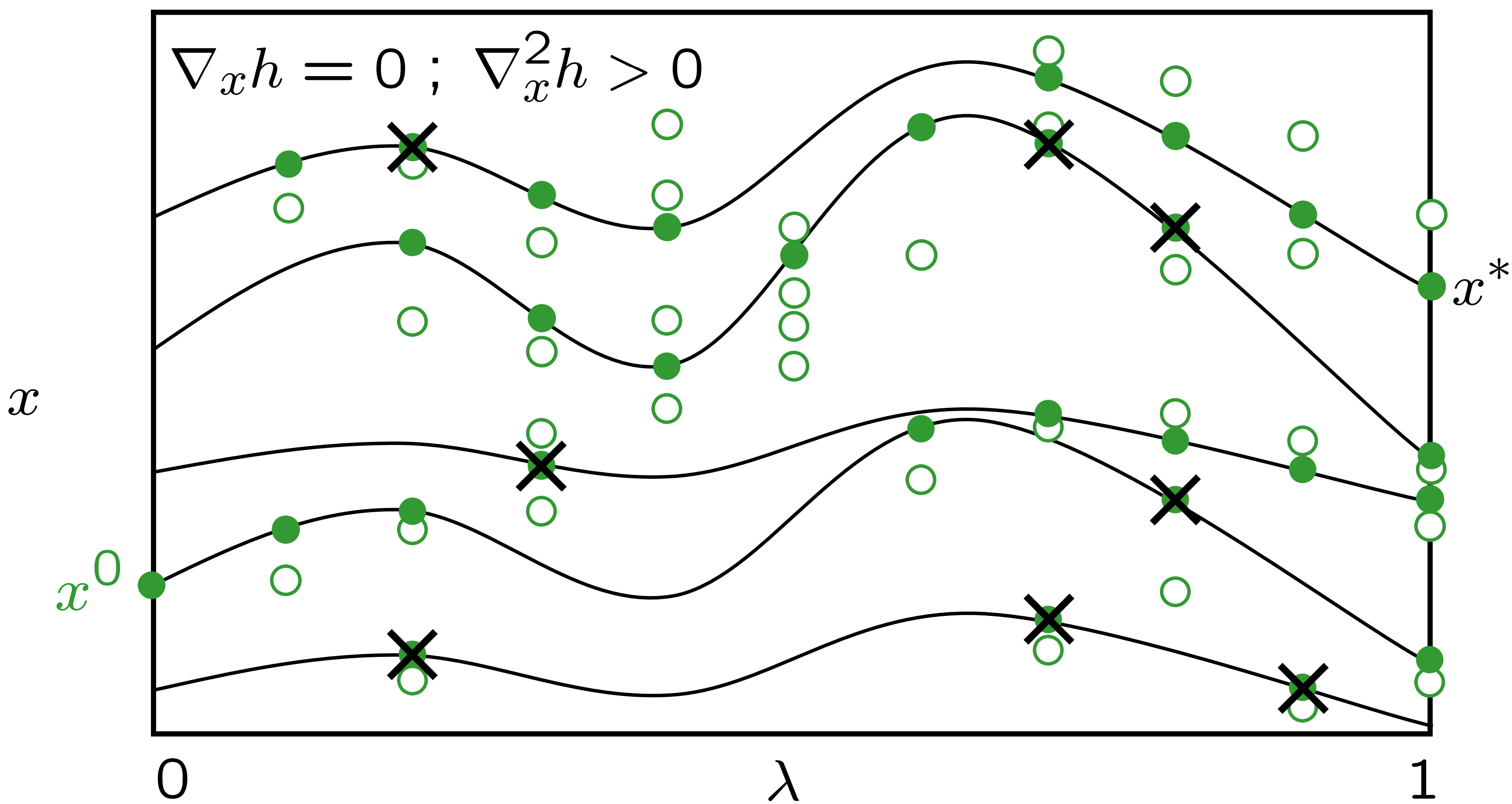
Homotopy Optimization using Perturbations & Ensembles (HOPE)

- Improvements over HOM
  - Produces ensemble of sequences of local minimizers of $h(x, \lambda)$ by perturbing intermediate results
  - Increases likelihood of predicting global minimizer
- Algorithmic considerations
  - Maximum ensemble size
  - Determining ensemble members

Illustration of HOPE

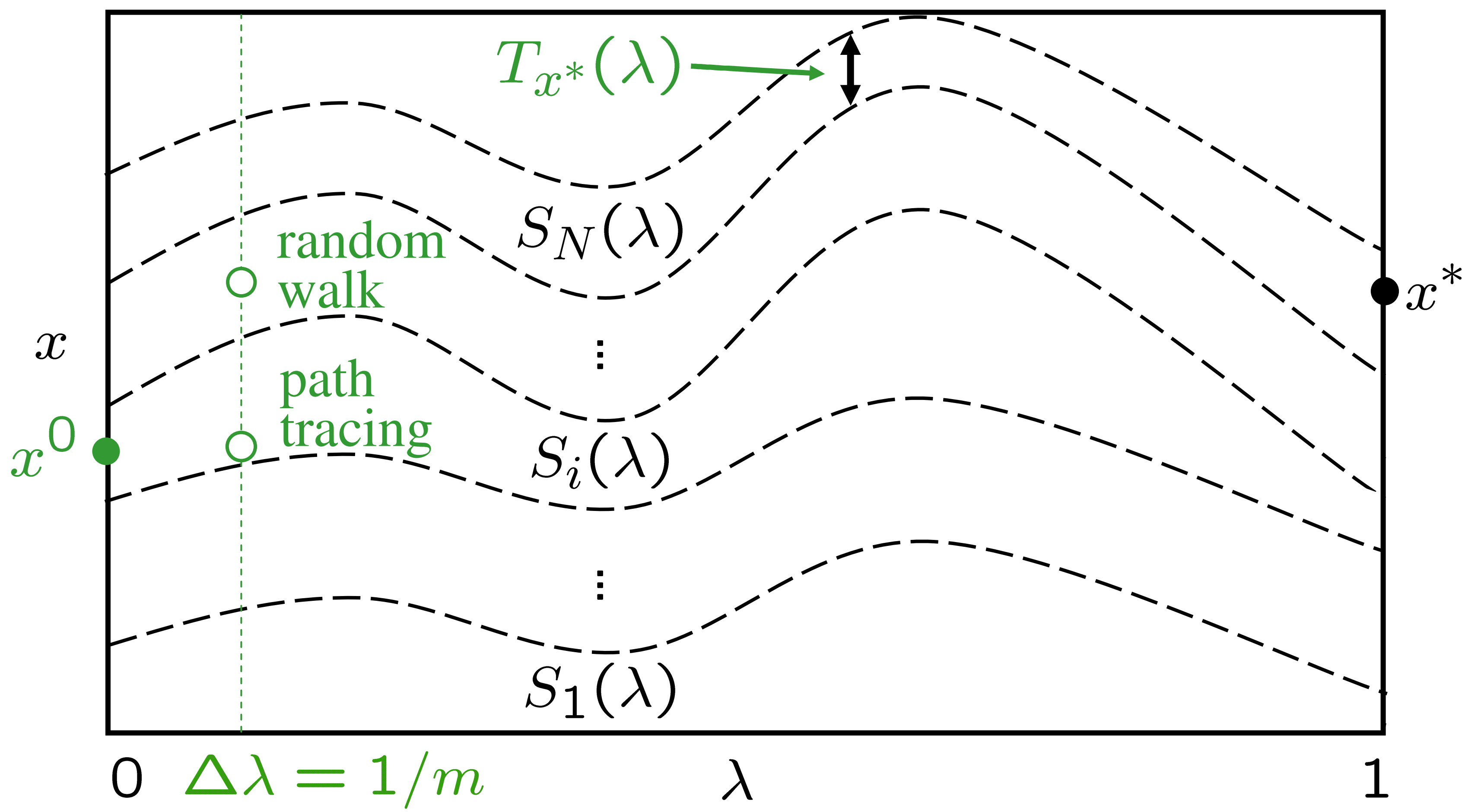
Constraint: ensemble size $\equiv |\mathbb{E}| \leq 2$

$$x^* = \min_{x\in\mathbb{R}} f_1(x) \qquad h(x,\lambda) = (1-\lambda) f_0(x) + \lambda f_1(x)$$



Convergence of HOPE

Goal: $m \in \mathbb{Z}^{+}$ s.t. $\mathcal{P}(\exists x \in \mathbb{E}_m \big| x \in S_N) > \rho$



Convergence of HOPE

$$\alpha = \min_{\lambda \in [0,1]} \{T_{x^*}(\lambda)\} \qquad P = \begin{bmatrix} 1-2\alpha & \alpha & & & \alpha \\ \alpha & 1-2\alpha & \alpha & & \\ & \ddots & \ddots & \ddots & \\ & & \alpha & 1-2\alpha & \alpha \\ \alpha & & & \alpha & 1-2\alpha \end{bmatrix}$$

No constraints on ensemble size: $|\mathbb{E}_m| = 2^m$

$\mathbb{E}_0 = \left\{x^0\right\}$; $\mathbb{E}_k = \mathbb{E}_{k-1} \cup \{\text{perturbed versions of } \mathbb{E}_{k-1}\}$

$$\begin{aligned} \mathcal{P}(\exists x \in \mathbb{E}_m : x \in S_N) &= 1 - \prod_{k=0}^{m} \left(1 - e_i^T P^k e_N\right)^{\binom{m}{k}} \\ &\geq 1 - \prod_{k=\kappa}^{m} \left(1 - P^k_{N/2,N}\right)^{\binom{m}{k}} \qquad (\kappa = \min\{i, N-i\}) \\ &= 1 - \prod_{k=\kappa}^{m} \left(1 - \frac{1}{N} \sum_{l=0}^{N-1} (-1)^l \left(1 - 2\alpha + 2\alpha \cos\left(\frac{2\pi l}{N}\right)\right)^k\right) \end{aligned}$$

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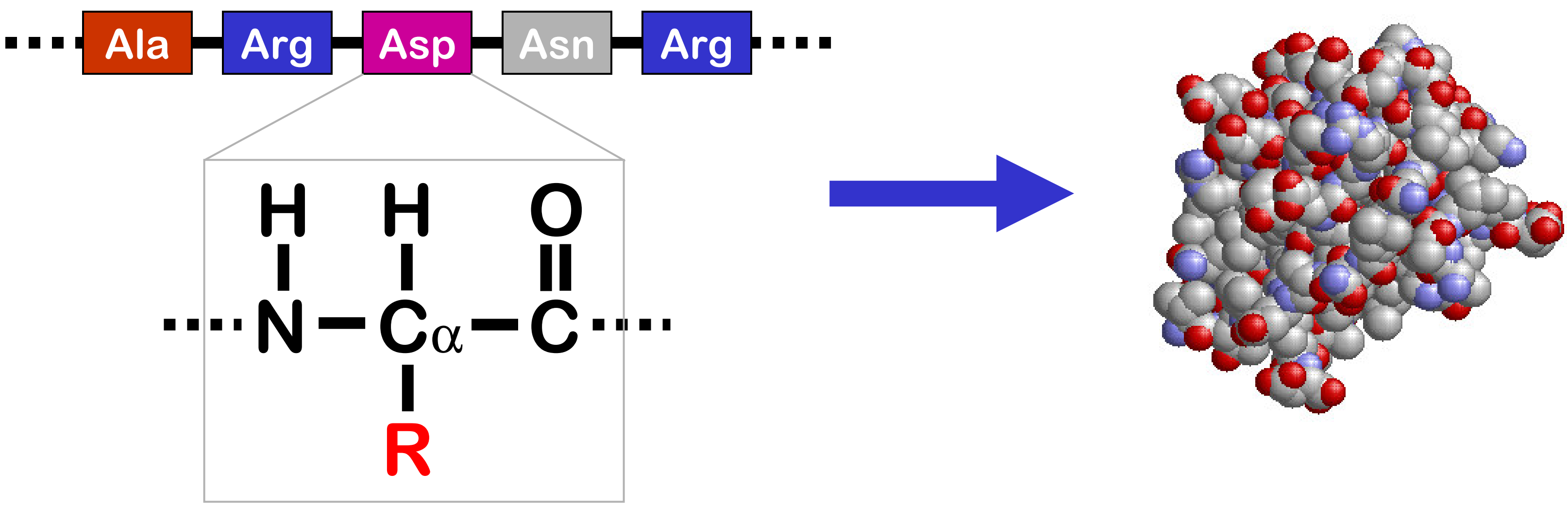
Protein Structure Prediction

Amino Acid Sequence   Protein Structure



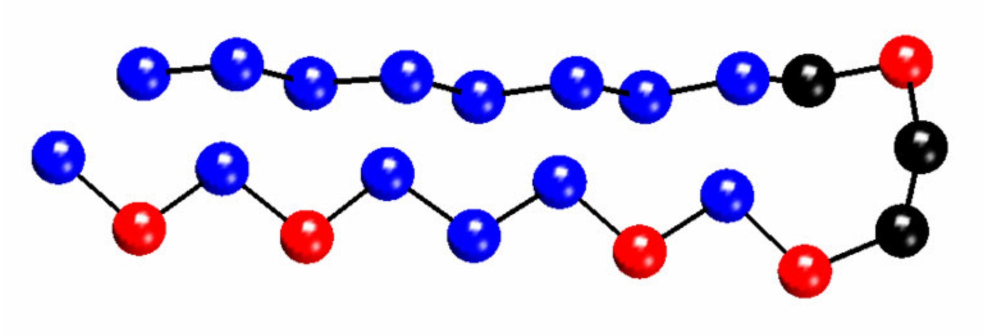
Given the amino acid sequence of a protein (1D), is it possible to predict its native structure (3D)?

Protein Structure Prediction

- Given:
  - Protein model
    - Molecular properties
    - Potential energy function (force field)
- Goal:
  - Predict lowest energy conformation
    - Native structure [Anfinsen, 1973]
  - Develop hybrid method, combining:
    - Energy minimization [numerical optimization]
    - Comparative modeling [bioinformatics]
      - Use **template** (known structure) to predict **target** structure

Protein Model: Particle Properties

- Backbone model
  - Single chain of particles with residue attributes
  - Particles model C_α atoms in proteins



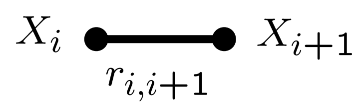
- Properties of particles
  - Hydrophobic, Hydrophilic, Neutral
  - Diverse hydrophobic-hydrophobic interactions

[Veitshans, Klimov, and Thirumalai. *Protein Folding Kinetics*, 1996.]

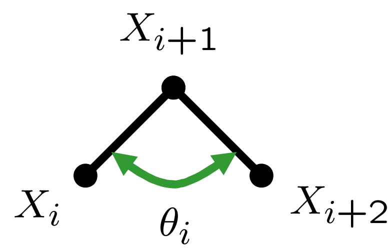
Protein Model: Energy Function

$$E(X) = E_{bl}(X) + E_{ba}(X) + E_{dih}(X) + E_{non}(X)$$

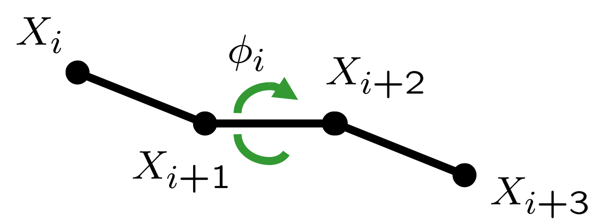
$$E_{bl}(X) = \sum_{i=1}^{n-1} \frac{k_r}{2} \left(r_{i,i+1} - \bar{r}\right)^2$$



$$E_{ba}(X) = \sum_{i=1}^{n-2} \frac{k_\theta}{2} \left(\theta_i - \bar{\theta}\right)^2$$



$$E_{dih}(X) = \sum_{i=1}^{n-3} \left[A_i(1 + \cos\phi_i) + B_i(1 + \cos 3\phi_i)\right]$$



$$E_{non}(X) = \sum_{i=1}^{n-3} \sum_{j=i+3}^{n} \gamma_{ij} \left\{ \alpha_{ij} \left(\frac{\bar{r}}{r_{ij}}\right)^{12} - \beta_{ij} \left(\frac{\bar{r}}{r_{ij}}\right)^{6} \right\}$$

Homotopy Optimization Method for Proteins

- Goal
  - Minimize energy function of target protein

$$\min_{X \in \mathbb{R}^{3n}} E^1(X), \qquad (E^1 : \mathbb{R}^{3n} \to \mathbb{R})$$

- Steps to solution
  - Energy of template protein: $E^0(X^0) = \min_{X \in \mathbb{R}^{3n}} E^0(X)$
  - Define a homotopy function:
    - $H(X, \lambda) = \rho^0(\lambda) E^0(X) + \rho^1(\lambda) E^1(X)$
    - Deforms template protein into target protein
  - Produce sequence of minimizers of $H(X, \lambda)$ starting at $\lambda = 0$ and ending at $\lambda = 1$

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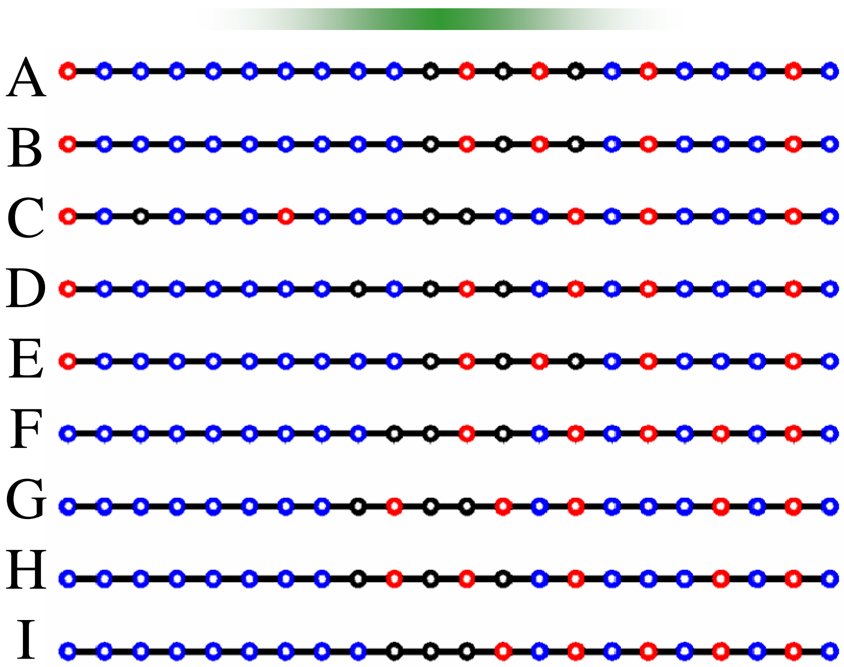
Numerical Experiments

9 chains (22 particles) with known structure

Loop Region

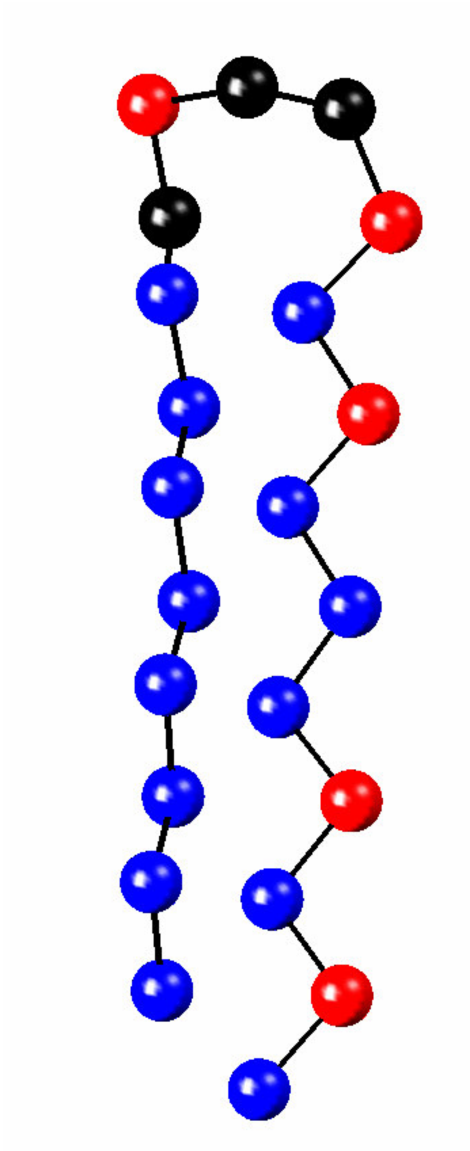


Hydrophobic **Hydrophilic** **Neutral**

Sequence Matching (%)

	A	B	C	D	E	F	G	H	I
A	100								
B	77	100							
C	86	91	100						
D	91	86	77	100					
E	73	82	73	82	100				
F	68	68	**59**	77	86	100			
G	68	68	**59**	77	86	**100**	100		
H	68	68	**59**	77	86	**100**	**100**	100	
I	73	59	64	68	77	73	73	73	100

Numerical Experiments



Numerical Experiments

- 62 template-target pairs
  - 10 pairs had identical native structures
- Methods
  - HOM vs. Newton's method w/trust region (N-TR)
  - HOPE vs. simulated annealing (SA)
    - Different ensemble sizes (2,4,8,16)
    - Averaged over 10 runs
    - Perturbations where sequences differ

Ensemble SA
Basin hopping
$T_0 = 10^5$
Cycles = 10
Berkeley schedule

- Measuring success
  - Structural overlap function: $0 \leq \chi \leq 1$
    - Percentage of interparticle distances off by more than 20% of the average bond length ($\overline{r}$)
  - Root mean-squared deviation (RMSD)

Results

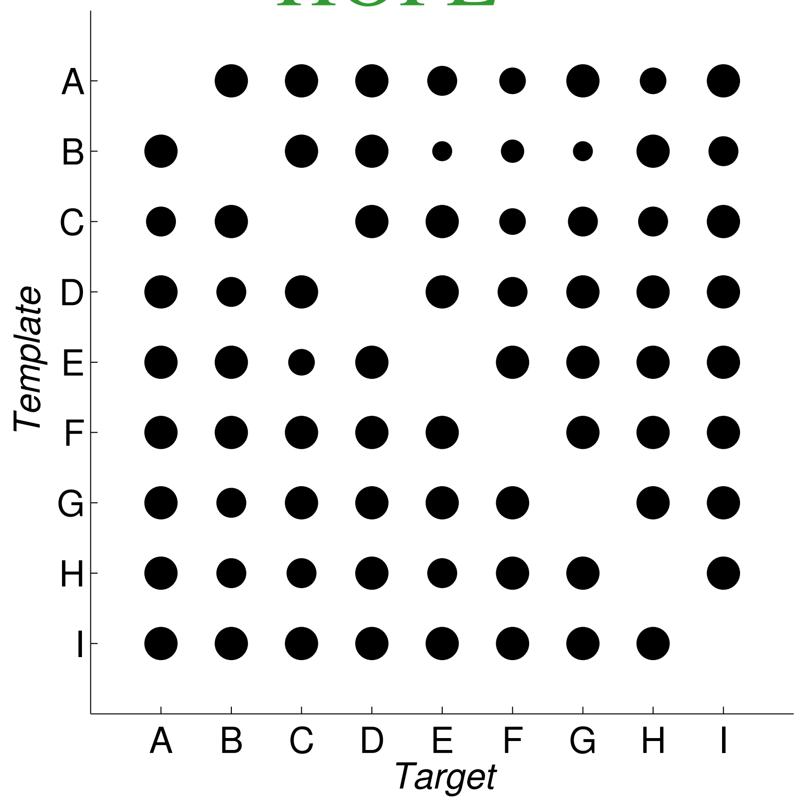
Method		χ = 0	Success	Mean χ	Mean RMSD	Time (sec)
HOM		**15**	**0.24**	**0.36**	**0.38**	**10**
N-TR		4	0.06	0.45	0.55	1

Method	Ensemble Size	χ = 0	Success	Mean χ	Mean RMSD	Time (sec)
HOPE	2	33.40	0.54	0.14	0.17	35
	4	43.10	0.70	0.08	0.11	65
	8	54.60	0.88	0.03	0.04	115
	16	**59.00**	**0.95**	**0.01**	**0.02**	**200**
SA	2	13.10	0.21	0.27	0.36	52
	4	20.80	0.34	0.19	0.26	107
	8	28.50	0.46	0.13	0.19	229
	16	40.20	0.65	0.08	0.12	434

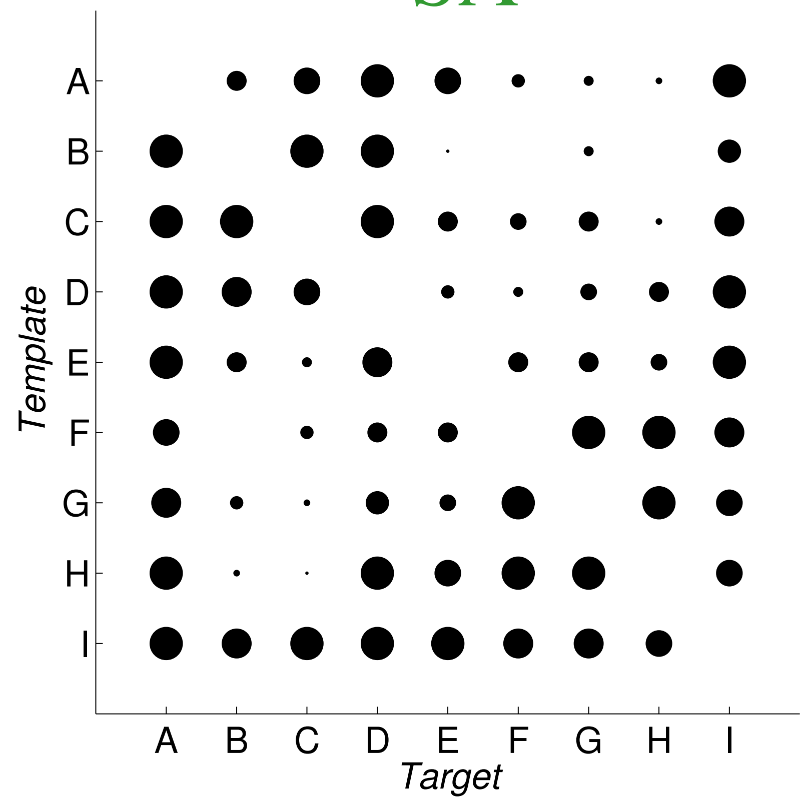
Results

Success of HOPE and SA with ensembles of size 16 for each template-target pair. The size of each circle represents the percentage of successful predictions over the 10 runs.

HOPE



SA



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Conclusions

- Homotopy optimization methods
  - More successful than standard minimizers
- HOPE
  - For problems with f^0, x^0 (E^0, X^0) readily available
  - Solves protein structure prediction problem
  - Outperforms ensemble-based simulated annealing
    - No fine tuning of SA

HOPEful Directions

- Protein structure prediction
  - Protein Data Bank (templates), TINKER (energy)
  - Probabilistic convergence analysis ($\mathbb{R}^n$)
- HOPE for large-scale problems
  - Inherently parallelizable
  - Communication: enforce maximum ensemble size
- Sandia
  - Protein structure prediction (Bundler)
  - LOCA, APPSPACK
  - SGOPT

Other Work/Interests

- Optimization
  - Surrogate models in APPSPACK (Sandia)
- Linear Algebra
  - Structure preserving eigensolvers
    - Quaternion-based Jacobi-like methods
  - RF circuit design – efficient DAE solvers
    - Preconditioners, harmonic-balance methods
- Information processing/extraction
  - Entity recognition/disambiguation
    - Persons, locations, organization
  - Querying, clustering and summarizing documents

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